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Predictive values of TIA referrals from first-contact healthcare: Systematic review

Kandiyali, R[1] Lasserson, D[2,3], Whiting, P[1,4], Richards, A[4]. Mant, J[5].

1. School of Social and Community Medicine, University of Bristol, BS2 8HW

2. NIHR Oxford Biomedical Research Centre, Department of Geratology, Oxford University Hospitals NHS Foundation Trust, Headley Way, Oxford. OX2 9DU

3. Nuffield Department of Medicine, University of Oxford, Old Road Campus, Headington, Oxford. OX3 7LF

4. NIHR CLAHRC West, University Hospitals Bristol NHS Foundation Trust, 9th Floor, Whitefriars, Lewins Mead, Bristol BS1 2NT

5. General Practice and Primary Care Research Unit, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge, CB2 0SR

Corresponding author: rebecca.kandiyali@bristol.ac.uk

ABSTRACT

Background Over 150,000 suspected TIAs are referred to outpatient clinics in England each year, the majority by GPs.

Aim To identify how many patients referred to TIA clinic actually have TIA (i.e. calculate the positive predictive value of first-contact healthcare referral) and to record the alternative diagnoses in patients without TIA.

Design and setting Systematic review. TIA clinic referrals from first-contact healthcare (GPs and Emergency Department doctors).

Method Four databases were searched using terms for TIA and diagnostic accuracy. Data on the number of patients referred to TIA clinic that actually had a TIA (positive predictive values) were extracted. Frequencies of differential diagnoses were recorded, where reported. Study quality was assessed using the QUADAS-2 tool.

Results Nineteen studies were included and reported sufficient information on referrals from GPs and EDs to derive positive predictive values (PPVs) (n=19,640 referrals). PPVs for TIA ranged from 12.9 to 72.5%. A formal meta-analysis was not conducted due to heterogeneity across studies. In those not diagnosed with TIA, about half of the final diagnoses were neurological or cardiovascular conditions.

Conclusion This study highlights the variation in prevalence of true vascular events in patients referred to TIA clinics. For patients without a cerebrovascular diagnosis, the high prevalence of conditions that also require specialist investigations and management are an additional burden on a care pathway that is primarily designed for prevention of recurrent stroke. Commissioners of services need to assess if the existing outpatient provision is optimal for people with pathologies other than cerebrovascular disease.

Keywords *ischemic attack, transient; stroke; diagnosis; predictive value of tests; primary health care; general practitioners*

How this fits in

The PPV of a TIA clinic referral has previously been described in selected populations in single studies. We conducted a systematic review and found that 12.9 to 72.5% of clinic referrals had a confirmed TIA and was usually above 50% when a composite (TIA or minor stroke) reference standard was used. Alternate diagnoses suggest that the total population with transient neurological symptoms may represent a susceptible population for further investigations and treatment which is not presently discussed in UK Stroke and TIA guidance. Commissioners should ensure that TIA services can meet the needs of a heterogenous patient group.

INTRODUCTION

A transient ischaemic attack (TIA) is a temporary focal neurological disturbance due to an interruption in the blood supply to an area of the brain. (1) We use the term transient neurological symptoms to describe the broad range of symptoms that may occur following a TIA or another condition that may mimic TIA. There is no ‘gold standard’ clinical test that can be used to diagnose a TIA or stroke based on symptomology. The diagnosis of TIA is based on the assessment of symptoms and ‘adequate’ investigation by a clinician. Historically TIA symptoms would need to resolve within 24 hours to be classified as TIA and not a minor stroke; however, in 2009 a tissue-based definition of TIA was proposed: ‘Transient ischemic attack (TIA): a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction’. (1, 2) In practice

however, the time-based definition may be the more operable, working definition, because identification of infarcts requires imaging and not all TIA clinic attendees are imaged.

The incidence of transient neurological symptoms is high, estimated at 190 cases per 100,000 population (3)and clinic referral rates in the order of about 16 per 10,000 patients every year. (4) Outpatient TIA clinics are well equipped to identify and treat TIA and minor stroke, but only a proportion of suspected TIA cases will be confirmed. Those not presenting with a TIA may nevertheless suffer adverse health consequences. (5) The clinical assessment for TIA can be complex as the symptoms are transient and there are no persisting signs on examination to guide the referring clinician. There has been one previous brief review of predictive values in TIA, but an update is timely as there has been more published data to inform estimates of accuracy as well as richer data on alternative diagnoses in this complex clinic population. (6) The objective of our study was to evaluate the positive predictive values associated with first-contact healthcare referral, i.e. from General Practice (GP) or from an Emergency Department (ED), to TIA clinic and to describe the alternative diagnoses in referred patients.

METHODS

Data sources

Four databases (MEDLINE, EMBASE, and The Cochrane Database of Systematic Reviews and Database of Reviews and Effectiveness) were searched from 1989 to week 28, 2016 using terms for "TIA" combined with a diagnostic filter (supplementary file A1). We used the Bachmann filter (adapted to run on each database) which has been identified as one of the most sensitive diagnostic filters available, with acceptable precision (7). Additional papers were sought by screening the citations of retrieved studies. All data screening, extraction and full text assessment was done by a single reviewer and checked in detail by a second.

Inclusion criteria

Primary studies of any design, conference abstracts and systematic reviews reporting information necessary to derive positive predictive values of TIA diagnosis from first-contact healthcare (primarily GPs or ED doctors). Where more than one study reported the same predictive values, duplicate values were not reported. Where there was a duplication of reporting, preference was given to full-text studies which report the most detail with respect to the application of the index test and reference standard.

Data Extraction and Quality Assessment of Studies

Data were extracted on the type of study, geographic location, method for patient selection, age of the population and number of patients included in the study. We collected information on the positive and negative diagnoses, along with frequencies of unverified diagnoses, which reference standard the study applied (TIA alone or TIA and minor stroke), and what definition of TIA was used (tissue or time-based). Systematic reviews were identified as a source or relevant studies. QUADAS-2 was used to assess the risk of bias and applicability of included studies (8). We also recorded the frequencies of differential diagnoses for false positive TIAs. The details of all non TIA/stroke diagnoses were tabulated.

Statistical analysis and synthesis

For each study we calculated the PPV as number of true positives divided by the sum of true and false positives (i.e. the total number of patients referred to the clinic). The binomial exact standard errors were calculated where the standard error of the PPV was not reported. Due to high unexplained variation in the underlying prevalence of TIA, we chose not to estimate summary PPV. Forest plots were used to display the individual study estimates of PPV together with 95% CIs analysing the target conditions (TIA and the composite outcome of TIA and minor stroke) separately. While our main analysis reports results for full texts only, we carried out a sensitivity analysis including conference abstracts to examine the robustness of our results.

RESULTS

The search identified 3,924 unique records. Of these, 19 full texts met the eligibility criteria (Figure 1). Twelve conference abstracts also met inclusion criteria; these were included in the sensitivity analysis. Study characteristics are presented in Table A2.

Figure 1

Nine studies were conducted in the UK, three in Ireland, three in Australia, two in Portugal and one in each of Spain and France. All patients identified were TIA clinic referrals/attendees, using consecutive or all referrals within a given timeframe. 19 studies provided sufficient information to calculate the PPV for at least one of the reference diagnoses (TIA and or the composite reference diagnosis of TIA and minor stroke). The number of suspected TIAs referred from or including GPs (18/19 studies included this route) ranged from 52 to 3533 clinic attendees (Table A2). (9, 10)

Specialist diagnosis (reference standard)

In all cases, the reference standard was the clinical diagnosis of the stroke physician in clinic. Several studies reported that the assessment of TIA was standardised at their clinic, and/or of additional retrospective notes review to confirm the diagnosis made by a senior stroke/vascular specialist. Studies dichotomised diagnoses into two outcomes (TIA, which sometimes included minor stroke) and not TIA. All studies with the exception of a conference abstract included in the sensitivity analysis (11) where the tissue-based definition was used, used the time-based definition of TIA even where the later tissue-based definition was available.

Differential diagnoses

Twelve of the included studies reported on the final diagnoses received by patients, although one study did not report sufficient information to determine frequencies for all alternate diagnoses. (12) Where reported, the frequency of alternative diagnoses are shown in Table A3.

The range of conditions diagnosed includes diseases which have NICE guidance recommending assessment by an appropriately trained specialist such as multiple sclerosis, epilepsy and cardiac arrhythmias. The commonest diagnoses were seizure, syncope, transient global amnesia, tension headache and migraine (Table A3).

Unexplained diagnoses

The majority of studies did not provide clear information on the number of patients for whom there was no clear diagnosis following referral to a TIA clinic. (Table A3). Several studies had a "possible TIA" category (13, 14) with symptoms which were broadly consistent with, but not clearly diagnostic for TIA; and "non-TIA" when this was not the case. Since the diagnosis was essentially unconfirmed in these cases, our analysis treats possible TIA as essentially unexplained i.e. negative cases in our analysis of PPV.

Positive predictive values of TIA from first-contact healthcare

The proportion of referred patients with a final diagnosis of TIA and/or minor stroke ranged from 22.0 to 77.9% (figure 2), and ranged from 12.9 to 68.6% of patients with a final diagnosis of TIA (figure 3). However, the distribution of PPV estimates appear to differ depending on the reference standard as 13/18 studies have a PPV ≥ 50% for a combined TIA and minor stroke outcome but only 4/18 studies have a PPV ≥ 50% when the reference standard was just TIA.

Assessment of study quality

Application of the QUADAS-2 checklist yielded similar results across studies, with all studies having a high risk of bias in the reference standard domain. The bias relates to the absence of a "gold standard" test and that the diagnostician knows that the patients were referred as suspected TIA (as all patients were seen in routine TIA clinics).

Influence of referral source and referral criterion

The majority of studies included all referrals and did not report on the composition of referrals (GP or ED) and/or provide sufficient data to calculate PPVs by referral source. It is plausible that studies may have included referrals from other sources such as ophthalmology, and secondary care, but reporting on this issue was scant. Two studies (9, 15) provided sufficient information to calculate PPVs according to two referral routes (GP or ED) and a further study provided this information on PPVs for referrals purely from GPs (16). A further study gave PPVs predominantly from an ED setting (17), whereas all other studies appear to have largely comprised referred from GPs. With the exception of one small study (9), the PPVs appear lower in GP referrals than in referrals from ED. Only one study which restricted itself to suspected anterior circulation TIA events (18), described specific referral criteria.

Figure 2, Figure 3

Impact of including conference abstracts

In general, interpretation of the results did not change when conference abstracts were included (figure A4, A5), however, Kleinig et al. (11) had much lower PPVs for both TIA (7.1% CI: 3.9-11.6) and the combined outcome (16.7 CI: 11.7-22.6). This study was set in an MRI-based referral clinic using the tissue-based reference standard.

Discussion

Summary of key findings:

Our review has identified considerable variability in PPVs for TIA across studies. The subset of studies we identified which report on alternative diagnoses highlights the predominance

of additional neurological and cardiological diseases which are TIA mimics requiring specialist assessment either within the TIA service or at a subsequent specialty clinic attendance. While our review demonstrates a variation in PPVs across studies, it could be that this is explained by a combination of referral source and diagnostic criteria, study age and/or the cardiovascular event being diagnosed. For instance, we found some evidence to suggest that PPVs in Primary Care populations may be lower than in those which included ED. However, inference about the possible influence of referral source and referral criterion is difficult because of other study differences. PPVs also tended to be higher in studies conducted in recent years, which might reflect a change in operation of the diagnostic criteria and improving recognition of symptoms by doctors over time. Finally, studies which included stroke had higher PPVs; this might reflect the broader diagnostic criteria or that GPs and ED doctors may be more likely to correctly identify a stroke due to the persistent nature of the deficit.

Strengths and limitations: Since there was no assessment of patients not thought by first-contact health care to have suffered a TIA, we do not know how many people with TIAs were missed. Therefore, we cannot compute sensitivity or specificity. This means that we cannot interpret whether high predictive values were associated with higher referral thresholds (which is likely to be associated with lower sensitivity, i.e. more TIAs missed by first-contact health care). It also means that we cannot compute prevalence of TIA in the population seen by first-contact health care, which is a key determinant of predictive value.

While we think the reference standard is acceptable – in all cases it was analogous to how diagnoses are made in practice – specialists were not blind to the index GP/ED diagnosis. This might foreseeably lead to more non-TIAs being misclassified as TIAs.

To explore potential publication bias, we included conference abstracts in a sensitivity analysis. Predictive values for TIA were similar, suggesting that publication bias is unlikely to be a major issue.

The PPVs we have reported are at study level i.e. across studies. Each study reflects practice of multiple clinicians, who may vary considerably. A PPV does not indicate whether the referral to TIA clinic was appropriate for the patient, and/or whether a more appropriate action should have been taken.

Interpretation in the light of existing literature: Whilst we were unable to determine measures of sensitivity and specificity, positive predictive values are a key statistic used in predictive risk modelling and the planning of prevention services. (19)
Our study found that PPVs for TIA are quite high (as compared with other conditions with fast-track referral) (20-22) but the key message is that TIA is an uncertain diagnosis. The use of PPVs as statistics for planning TIA services has been contested (23), as patients with transient symptoms that are not due to TIA have been recognized as a similarly morbid population to true TIA. (24-26) Clinical need is therefore not limited to confirmed TIAs but to the broader populace with transient symptoms. The dual findings of our review - relatively high but variable predictive values and a predominance of cardiovascular pathologies - suggests that active risk factor management, including early initiation of antiplatelet agents is still appropriate to mitigate early recurrent stroke risk after initial suspicion of TIA. (27)

Implications for research and practice: Our study shows that TIA specialist services need to handle a broad range of diagnoses, not just TIA. Many of the most common alternate diagnoses could benefit from appropriate specialty input and the challenge for commissioners of services is how best to deliver comprehensive care for patients who present with transient neurological symptoms. While the TIA clinic is well placed to manage the hyper-acute risk of recurrent stroke it may not be the optimal configuration in terms of specialist assessment for the range of neurological, cardiological and psychiatric conditions which also require ongoing care.

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Competing interests: The authors state that there are none.
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Figure 1: Study Flow

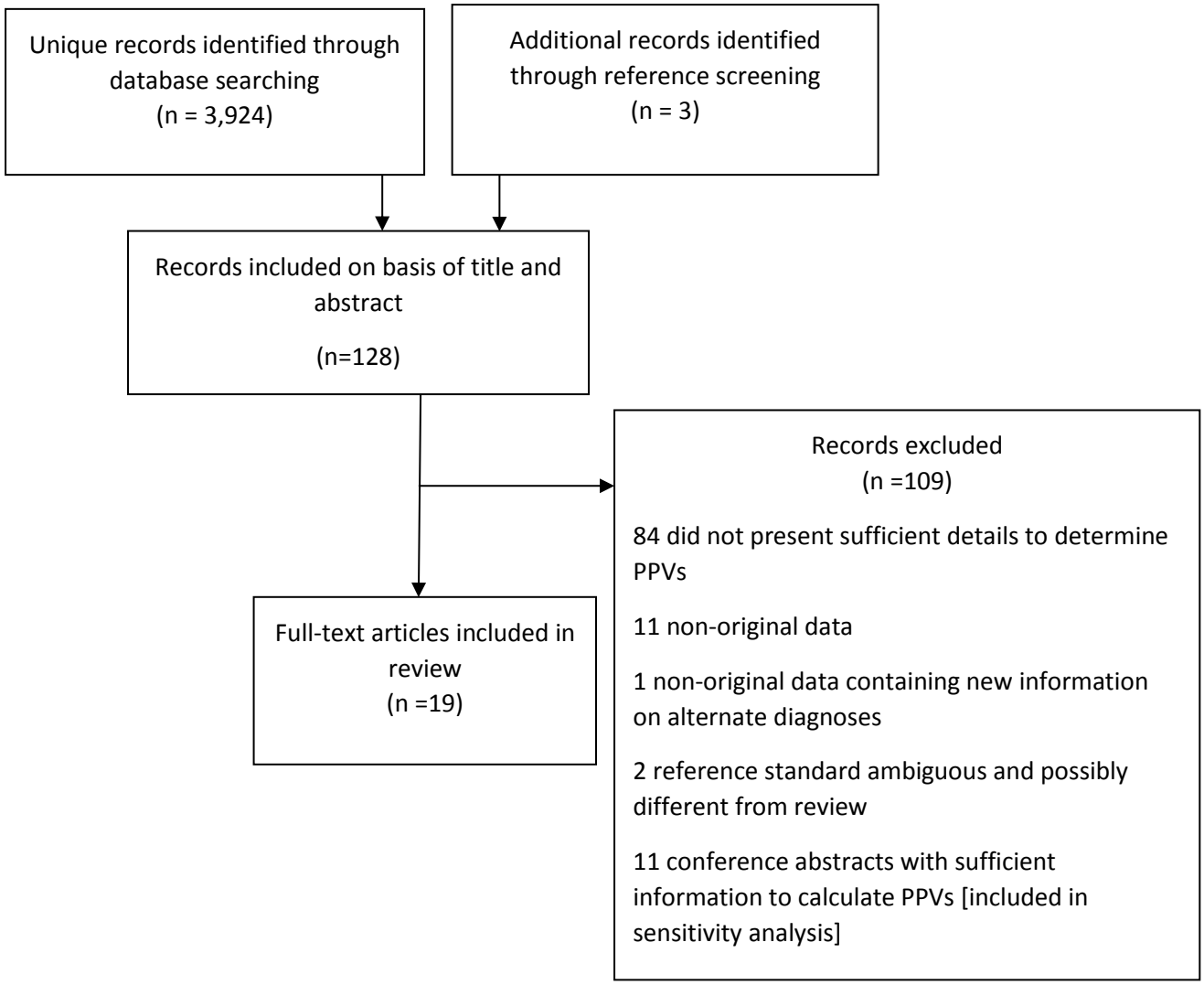


Figure 2: Positive predictive values of first-contact healthcare diagnosis in TIA and stroke

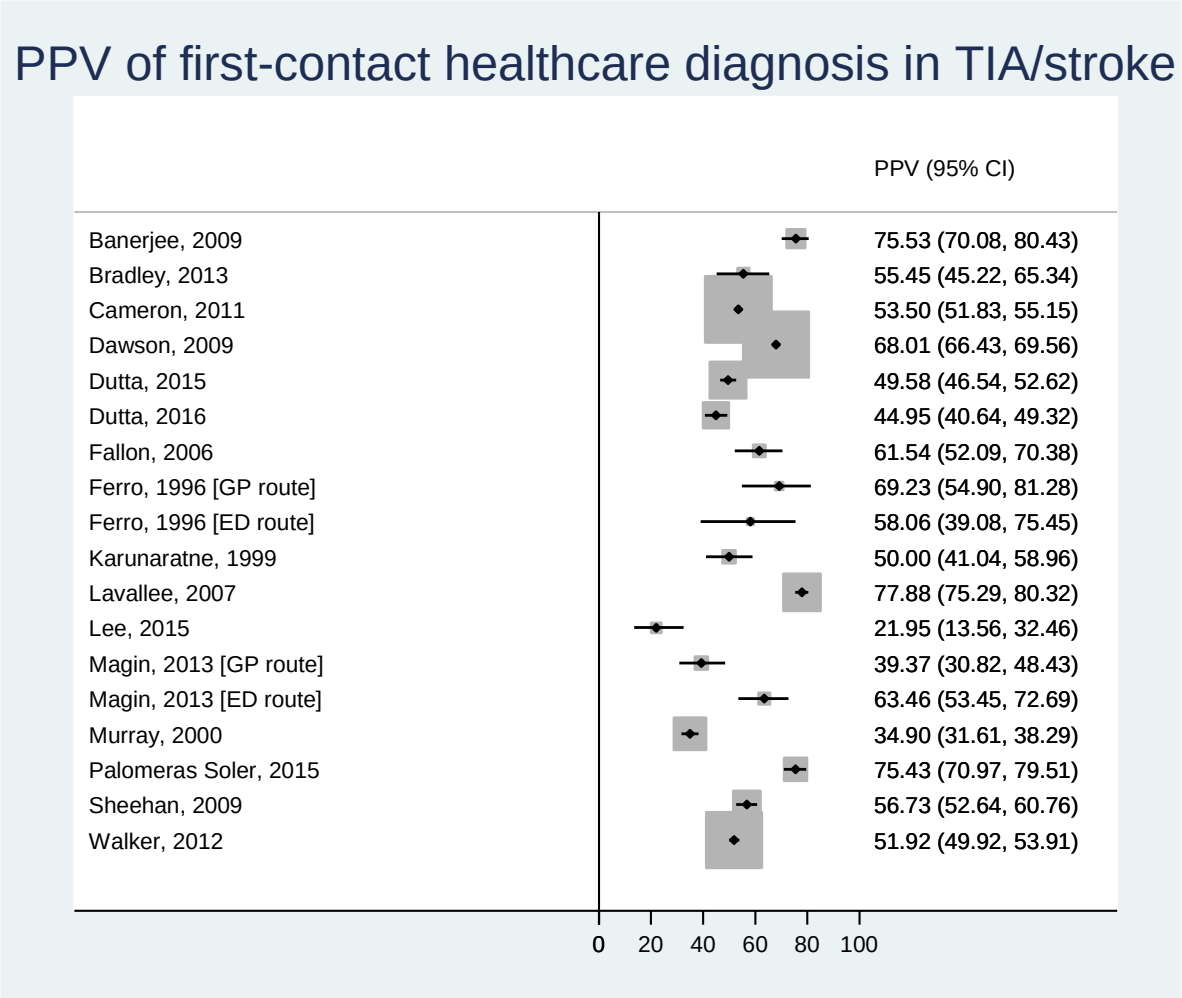


Figure 3: Positive predictive values of first-contact healthcare diagnosis in TIA

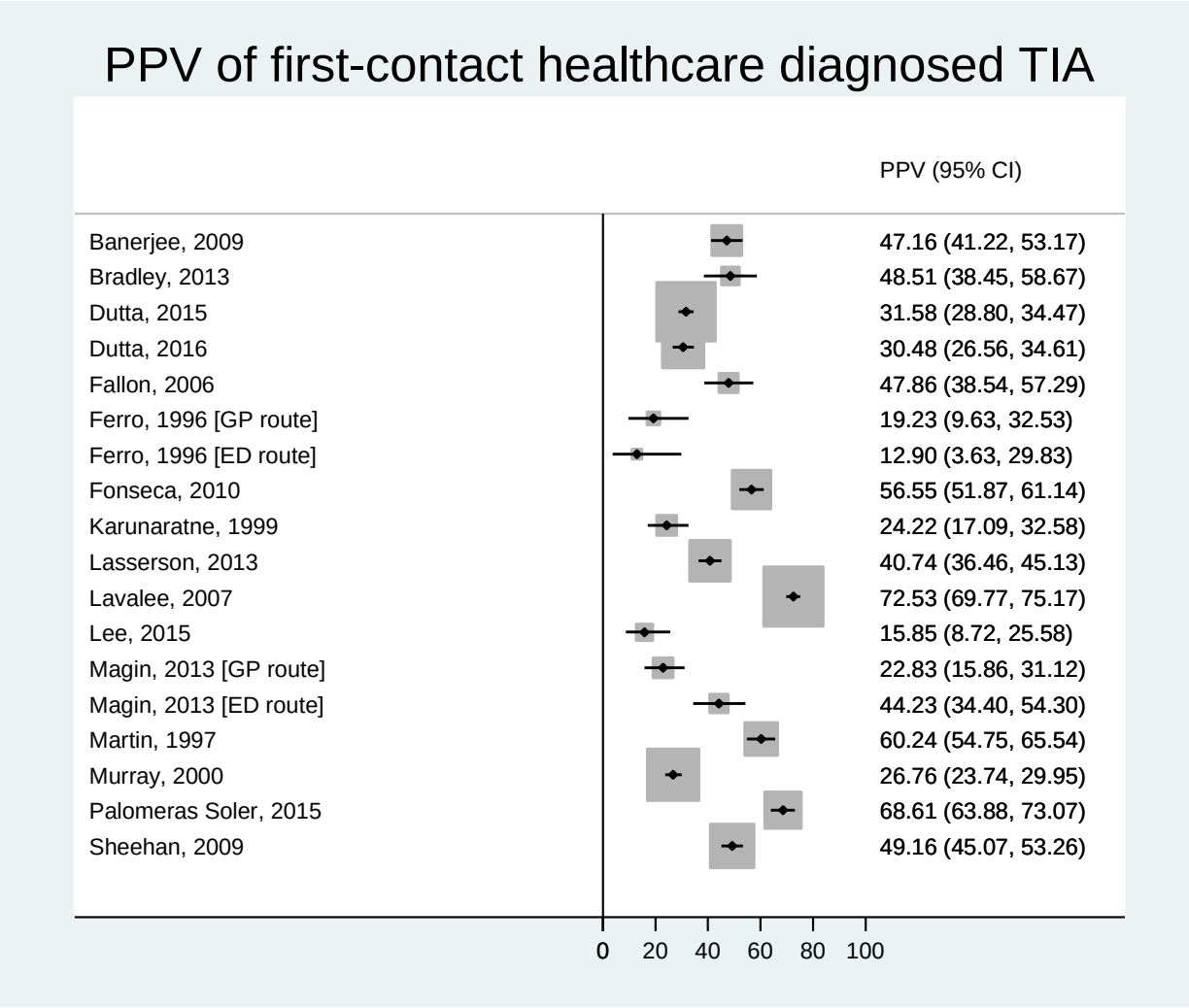


Table A2: Extracted data (stratified by referral route) for clinician accuracy[1]

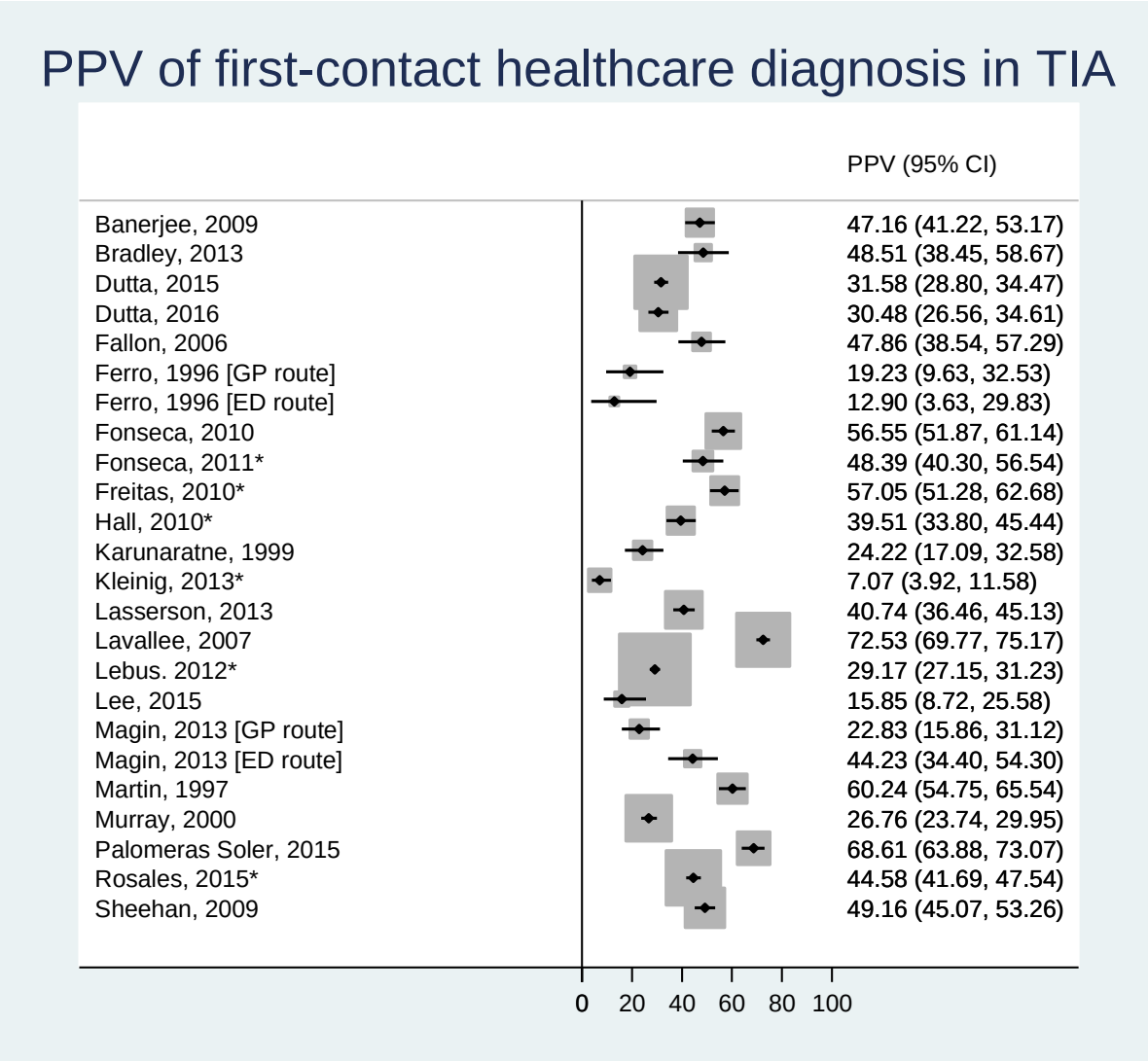
Study [country: region]	Type	Referral source	Mean age (sd)	TIAs	TIA or Stroke	Diagnosis unknown	Total, N	PPV for reference dx of TIA	PPV for reference dx of TIA & stroke
Banerjee et al, 2009(18) [England UK: London]	Prospective cohort†	GP & ED	68 (13.5)	133	213	2 unknown, 15 unavailable	282	47.2	75.5
Bradley et al, 2013(28) [Ireland: Dublin]	Prospective cohort	GP & ED	60 (14.3)	49	56	None	101	48.5	55.4
Cameron et al, 2011(10) [Scotland UK: Glasgow]	Prospective cohort	GP & ED	65 (13.6)	-	1890	None	3533	-	53.5
Dawson et al, 2009(29) [Scotland UK: Glasgow]	Prospective cohort	GP & ED	65 (12.8)	-	2358	None	3467	-	68.3
Dutta et al, 2016 (30) [England UK: Gloucester]	Prospective cohort – DOT validation cohort	GP & ED	71 (14.0)	160	236	None	525	30.5	45.0
Dutta et al, 2015(31) [England UK: Gloucester]	Prospective cohort	GP & ED	72‡ (IQR: 60-80)	337	529	None	1067	31.6	49.6
Fallon et al, 2006(32) [Ireland: Dublin]	Prospective cohort	ED (primarily) & other – not specified	75.5 (-)	56	72	18	117	47.9	61.5
Ferro et al, 1996(9) [Portugal: central and southern]	Prospective cohort	GP	-	10	36	None	52	19.2	69.2

[1] Where there is more than one data entry for a single study this reflects that the study provided sufficient information to calculate PPVs by different referral sources.
† PPVs only reported for suspected TIAs which were seen at an anterior circulation TIA clinic.
‡ median not mean reported

Study [country: region]	Type	Referral source	Mean age (sd)	TIAs	TIA or Stroke	Diagnosis unknown	Total, N	PPV for reference dx of TIA	PPV for reference dx of TIA & stroke
Ferro et al, 1996(9) [Portugal: central and southern]	Prospective cohort	ED	-	4	18	None	31	12.9	58.1
Fonseca et al, 2009(14) [Portugal: Lisbon]	Prospective cohort	GP & ED	65 (-)	259 definite TIA	-	109 cases recorded as "possible" TIA	458	-56.6	-
Karunaratne et al, 1999(33) [Scotland, UK, Scotland: Borders]	Prospective cohort	GP & ED	67 (14)	31	64	7 non-TIA with no clear diagnosis	128	24.2	50.0
Lasserson et al, 2013(34) [England UK: Oxford]	Prospective cohort	GP	73 (12.8)	209	-	None	513	40.7	-
Lavalee et al, 2007(13) [France: Paris]	Prospective cohort	GP & ED	No overall - median ages reported by final diagnosis alone	643 definite TIA	701	144 cases recorded as "possible TIA"	1085	72.5	77.9
Lee et al, 2015(35) [Australia: Melbourne]	Prospective cohort	GP & ED	67 (16.9)	13	18	4 non-TIA with no clear diagnosis	82	15.9	22.0

Study [country: region]	Type	Referral source	Mean age (sd)	TIAs	TIA or Stroke	Diagnosis unknown	Total, N	PPV for reference dx of TIA	PPV for reference dx of TIA & stroke
Magin et al, 2013(36) [Australia: Hunter New England]	Prospective cohort	GP	65 (15)	29	50	13 unclassified	127	22.8	39.4
Magin et al, 2013(36) [Australia: Hunter New England]	Prospective cohort	ED	65 (15)	46	66	9 unclassified	104	44.2	63.5
Martin et al, 1997(12) [England, UK: Liverpool]	Prospective cohort	GP & ED	62‡ (IQR: 23-94)	200	-	Unclear	332	60.2	-
Murray et al, 2007(4) [Scotland, UK: Glasgow]	Retrospective cohort	GP & ED	No overall. Age bands.	217	283	None	811	26.8	34.9
Palomeras Soler et al, 2015(37) [Spain: Barcelona]	Prospective cohort	GP & ED	-	282	310	None	411	68.6	75.4
Sheehan et al, 2009(38) [Ireland: Dublin]	Prospective cohort	GP & ED	69 (13)	292	337	None	257	49.2	56.7
Walker et al, 2012(39) [England, UK: Leicester]	Prospective cohort	GP & ED	-	-	1273	None	2452	-	51.9

Figure A5: PPV of first-contact healthcare diagnosis in TIA (sensitivity analysis including original data contained in conference abstracts).



*** Conference abstracts not included in main analysis.**